PLACENTAL TRANSFER OF TUBOCURARINE

Case Report

BY

P. O. OLDEN AND J. M. HARRIS

SUMMARY

A case is reported in which tubocurarine crossed the placental barrier and paralyzed a 28-week fetus. The mother was under treatment for status epilepticus. The authors review the present evidence for the transplacental passage of tubocurarine and suggest that previous work may not represent the situation accurately. Reference is made to a further case which also suggests transplacental passage of tubocurarine, this time in the first trimester of pregnancy.

Curare was first introduced into anaesthesia by Griffith and Johnson in 1942. As far as the writers are aware, there have been no reports of foetal depression from the use of tubocurarine in obstetrics. Following the work of Gray (1947), Whitacre and Fisher (1948), Pittinger, Morris and Keettel (1953), Cohen and associates (1953) and Crawford and Gardiner (1956), it has been accepted that the drug does not cross the placental barrier in sufficient quantities to cause paralysis of the foetus. Moya and Smith (1965), in their survey of the placental transport of drugs, point out that the placental barrier is relative rather than absolute. The authors feel that this is all too often forgotten, particularly so with the increase in the use of large and repeated doses of muscle relaxants and controlled pulmonary ventilation in the management of many disease conditions.

CASE REPORT

Female aged 29, weight before pregnancy 59 kg.

The patient was a known epileptic of 11 years standing. For 9 years the epilepsy was well controlled by the use of various doses of phenobarbitone, primidone (Mysoline) and phenytoin (Epanutin).

In July 1965 she became pregnant. Four months later the epilepsy escaped control and she was admitted to hospital in status epilepticus. On that occasion treatment with a methohexitone drip (0.2 per cent) rapidly brought the fits under control. The patient was discharged on phenobarbitone, primidone and phenytoin. At approximately the 28th week of pregnancy, she was readmitted to hospital in status epilepticus. On this occasion treatment with large doses of methohexitone and paraldehyde failed to control the fits and a methohexitone drip (0.1 per cent) was again started. After 16 hours she had received 3,000 mg of methohexitone. This dosage had caused severe respiratory depression and she was deeply unconscious.

Clinical examination at this time showed a cyanosed patient with a respiratory rate of 10 b.p.m. There were medium to coarse rales throughout her chest. Her blood pressure was 90/60 mm Hg, pulse 112 beats/min and body temperature 36.0°C. X-ray examination of her chest revealed collapse of her left lower lobe.

The patient was admitted to the Intensive Care Unit. On admission she was intubated with a nasal endotracheal tube (Portex) and pulmonary ventilation was controlled with an East-Radcliffe ventilator. Despite the severe central depression, she was having minor generalized fits every 10-12 minutes. In order to prevent these, an initial dose of tubocurarine 30 mg was given intravenously. Subsequently 15-30 mg doses were administered intramuscularly as necessary. In order to prevent the reappearance of the fits, it became necessary to administer tubocurarine approximately every 2 hours. All other medication was withdrawn but treatment with intra-muscular penicillin was started.

Assessment by the obstetricians showed that the patient was approximately 28 weeks pregnant. The foetal heart beat was regular at a rate of 130 beats/min. An occasional contraction of the uterus was noted and the question was raised as to whether she was prematurely in labour. Blood-gas analysis after 2 hours of mechanical ventilation showed that the patient had a marked respiratory alkalosis (pH 7.62, Pco₂ 15.5 mm Hg, HCO₃ 22.7 m.eqquiv/l). Ventilation was consequently reduced. Sixteen hours after admission to the Intensive Care Unit, the patient was delivered of a baby girl by breech extraction (nitrous oxide and oxygen anaesthesia was used for the delivery). The total dose of tubocurarine administered was 245 mg.

The baby weighed 920 g. It had a severe cleft palate and hare-lip deformity. No other abnormalities were noted. The apex beat was regular at 100 beats/min. The baby made no effort to breathe and showed no spontaneous activity of any kind. The child was therefore intubated with a neonatal endotracheal tube (Warne). Ventilation was controlled with 100 per cent oxygen via a T-piece. After 1 hour there was still no sign of any spontaneous activity. No drugs of any kind had been administered to the child. The question was now raised as to whether the infant might be curarized. It was suggested that a small dose of edrophonium could be tried. One and a half hours after birth, edrophonium 0.2 mg was injected through an umbilical catheter. The

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result was dramatic. Within a few seconds of injection the baby began to make vigorous movements and breathe spontaneously. Consequently atropine 0.02 mg and neostigmine 0.1 mg were administered through the catheter. The child was extubated and breathed spontaneously in an incubator in an oxygen-enriched atmosphere. Unfortunately the temperature of the child had fallen to 32.2°C, and despite efforts to maintain body temperature it died 5½ hours after birth. After the death of the child, 40 ml of blood were removed for curare assay.

Estimation of the acid-base state of the mother shortly after the birth of the baby, gave the following results: pH 7.42, Pco₂ 25 mm Hg, HCO₃ 19.2 m.equiv/l. Subsequent management of this patient is a long and complex story. It will not be discussed further here.

CURARE ASSAY

The postmortem blood from the baby was frozen, stored for 18 hours, and then biologically assayed for curare-like activity on the rat phrenic-nerve diaphragm preparation (Bulbring, 1946). The assay method used was that of Chou (1947). A hemidiaphragm was dissected out with the phrenic nerve intact and set up in a 25-ml organ bath containing a high potassium Ringer solution (NaCl 0.9, KCl 0.048, CaCl₂ 0.024, NaHCO₃ 0.05, dextrose 0.1, g/100 ml). The solution was maintained at 37°C and vigorously gassed with 95 per cent oxygen, 5 per cent carbon dioxide from a sintered glass disc oxygenator. The phrenic nerve was electrically stimulated once every 10 seconds at supramaximal voltage using bipolar electrodes and a square-wave stimulator (C. F. Palmer (London) Ltd.). The contractions of the diaphragm were recorded by a spring-lever writing on a smoked drum. Doses of a freshly prepared standard solution of tubocurarine (Burroughs Wellcome) were given at 10-minute intervals and allowed to remain in the bath for 3 minutes. These caused a marked reduction in the height of the contractions. The response recovered when the tubocurarine was washed out and the bath refilled with fresh Ringer solution.

It can be seen from figure 1 that the reduction of twitch height was proportional to the tubocurarine dose. The preparation was sensitive to 25 μg of tubocurarine added to the bath and even 10 μg caused a slight reduction in the contraction (fig. 2).

When 1.0 ml of control serum (human serum frozen and stored for 18 hours) was added to the bath, no reduction in twitch height was observed. When 1.0 ml of postmortem serum from the baby was added, a small but significant reduction occurred. This response was greater than that produced by 10 μg, but less than that produced by tubocurarine 20 μg (fig. 2 and table I). When 2.0 ml of the postmortem serum from the baby was added to the tissue, a marked reduction of twitch height occurred. The addition of two doses each of 50 μg of neostigmine (without washing out the serum) caused the progressive reduction of the twitch to be clearly arrested (fig. 3).

Although these results on their own are not conclusive, they suggest that the baby’s serum possessed quite considerable curariform activity. The percentage reduction in response given by the two doses of serum was compared with the response of the tissue to various doses of the standard solution of tubocurarine (table I). From this data the actual activity of the infant’s serum...
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appeared to be of the order of 14–15 µg of tubocurarine per ml, though the limits of error of this figure are likely to be large. This is the equivalent in clinical anaesthesia of administering to the child tubocurarine (1.2 mg/kg) assuming that all the dose given stays in the plasma. Bush (1963) in a review of muscle relaxants in paediatric anaesthesia, quotes doses of 0.6 mg/kg as being necessary to curarize a child for 30–45 minutes.

**DISCUSSION**

There is no doubt in the minds of the authors that the baby was curarized, the evidence of bioassay and the response clinically to anticholinesterase therapy being considered conclusive.

A review of the literature relating to the transplacental passage of tubocurarine reveals some
interesting facts. The main work quoted on this subject was reported by Gray (1947), Whitacre and Fisher (1948), Pittinger, Morris and Keettel (1953), Cohen and others (1953), and Crawford and Gardiner (1956).

The work by Gray (1947) and Whitacre and Fisher (1948) was based on clinical impressions of the foetus following Caesarean section. The doses of tubocurarine used were, by modern standards, low, namely 15–20 mg. The work of Pittinger, Morris and Keettel (1953) was based on a chemical method of assay. The six patients studied were curarized, but were delivered vaginally. The doses of tubocurarine used varied from 6 to 60 mg. It is felt that the results obtained by this technique are unlikely to be significant, as the blood from five blank control cases, upon assay, revealed greater quantities of tubocurarine than did the blood from some of the actual patients who had received the drug. Pittinger, Morris and Keettel themselves point out that these differences were not significant.

The work of Cohen and associates (1953), was based upon the administration of doses of tubocurarine between 18 and 42 mg. The tubocurarine concentration in the foetal blood was analyzed by a chemical method. In no case was any tubocurarine found in foetal cord blood.

The most recent work performed was by Crawford and Gardiner (1956). It is perhaps this work which is more widely quoted than any other. There were six cases in their series. The maternal doses of tubocurarine were 15 mg (three cases) and 20 mg (three cases). In only three of the six cases presented were they able to assay tubocurarine in the foetal cord blood. They were using a frog rectus preparation which would only tolerate 0.2 ml of plasma. In other words, a level of tubocurarine of 0.6 \( \mu g/ml \) of plasma means that the preparation was responding to 0.12 \( \mu g \) of tubocurarine. The fact that on other occasions they were unable to detect 0.5 \( \mu g/ml \) must surely mean they were at the limit of sensitivity of the preparations. There is no correlation in their results, as they themselves point out, between the dose given to the mother, and the concentration found in the foetal cord blood. From this study of the relevant literature it can be seen that very little is known about the placental transfer of tubocurarine.

The authors agree that for lower segment Caesarean section there can be no serious objection to the use of tubocurarine, even though this is based on clinical impressions. It must be remembered that all assays on foetal blood were, in fact, performed on foetal cord blood. The authors have found the pH of cord blood to be nearly always 7.20. The blood pH of a baby immediately after onset of spontaneous respiration is approximately 7.4. It has been shown that as the pH falls so the amount of free tubocurarine in the plasma rises (Baraka, 1964). The converse also applies. In other words, the change at birth of the foetus to a more alkaline blood pH would significantly lower the concentration of free tubocurarine in the plasma. The significance of this change is obvious.

It will be noted that the child in the case report was born at 28 weeks. With the increasing use of long-term controlled ventilation with tubocurarine for such conditions as tetanus, status epilepticus and even eclampsia, it is obviously important that we should know precisely the conditions under which tubocurarine crosses the so-called placental barrier. The question now arises as to whether tubocurarine crosses the placental barrier with equal facility at, say, 3 months or at term.

From strong circumstantial evidence it is almost certain that tubocurarine does cross the placental barrier in the first trimester of pregnancy.

A patient with tetanus was curarized and the lungs ventilated in the 8th to 12th weeks of pregnancy. She gave birth, at term, to a child suffering from arthrogryphosis multiplex congenita (Jago, 1966, personal communication). This disease can be produced experimentally in animals by paralyzing them in utero at a time when their joints are developing (Drachman and Coulombre, 1962).

It is hoped that this report will highlight the lack of real knowledge of the placental transport of the relaxant drugs. The term “placental barrier” is misleading and we would do well to remember that it is indeed only relative.

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REFERENCES


PASSAGE PLACENTAIRE DE TUBOCURARINE: RAPPORT D'UN CAS

SOMMAIRE
On rapporte un cas dans lequel la tubocurarine a franchi la barrière placentaire et paralysé un fœtus de 28 semaines. La mère était en traitement pour état de mal épileptique. Les auteurs examinent de nouveau l’évidence présente relative au passage transplacentaire de la tubocurarine et suggèrent qu’un travail précédent n’est pas en mesure de représenter la situation de façon précise. On se réfère à un cas ultérieur qui, lui aussi, suggère un passage transplacentaire de la tubocurarine, mais cette fois dans le premier trimestre de la gestation.

ZUSAMMENFASSUNG
Es wird ein Fall beschrieben, bei dem Tubocurarin die Plazentarschranke durchbrach und einen 24 Wochen alten Fetus lähmte. Die Mutter befand sich wegen Epilepsie in Behandlung. Die Autoren betrachten den vorliegenden Nachweis, daß Tubocurarin die Plazenta passieren kann, unter kritischen Gesichtspunkten. Sie sind der Ansicht, daß die frühere Untersuchung die tatsächliche Situation möglicherweise nicht genau darstellt. Bezug genommen wird auf einen weiteren Fall, der ebenfalls eine diaplazentare Passage von Tubocurarin vermuten läßt, diesmal im ersten Drittel der Schwangerschaft.